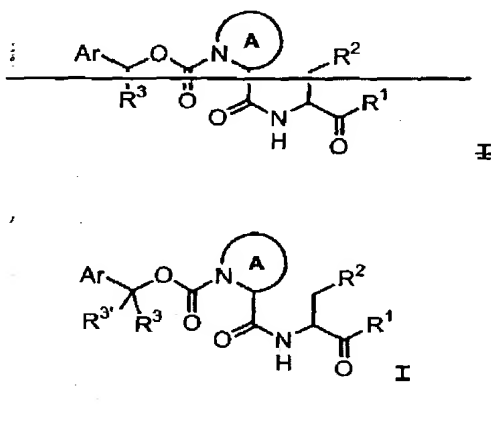


EXHIBIT A

Claim amendments presented in applicants' Amendment And Reply To Office Action, dated August 7, 2003, with omitted parentheticals "original" inserted for claims 5, 6, and 16 and "currently amended" inserted for 8, 12, 14, 15, and 17 (inserted text in bold, italics).

1. (previously amended) A compound of formula I:



wherein:

Ring A is an optionally substituted ~~piperidine~~, tetrahydroquinoline or tetrahydroisoquinoline ring;

R<sup>1</sup> is ~~hydrogen~~, -H, -CHN<sub>2</sub>, -R, or -CH<sub>2</sub>Y;

R is an optionally substituted group selected from an aliphatic group, an aryl group, an aralkyl group, a heterocyclic group, or an heterocyclylalkyl group;

Y is an electronegative leaving group;

R<sup>2</sup> is CO<sub>2</sub>H, CH<sub>2</sub>CO<sub>2</sub>H, or esters, amides or isosteres thereof;

Ar is an optionally substituted aryl group; and

R<sup>3</sup> is ~~hydrogen~~ -H, and R<sup>3</sup> is -H, an optionally substituted C<sub>1-6</sub> alkyl, -F<sub>3</sub>, CN, or aryl;

or R<sup>3</sup> is attached to Ar to form an unsaturated or partially saturated five or six membered fused ring having 0-2 heteroatoms; or

R<sup>3</sup> and R<sup>3</sup> are each -F.

2. (currently amended) The compound of claim 1 ~~having one or more of the following features:~~, wherein

~~(a) R<sup>1</sup> is CH<sub>2</sub>F;~~

~~(b) R<sup>2</sup> is CO<sub>2</sub>H or esters, amides or isosteres thereof;~~

~~(c) R<sup>3</sup> is hydrogen or an optionally substituted C<sub>1-6</sub> alkyl; and~~

~~(d) Ar is an optionally substituted aryl.~~

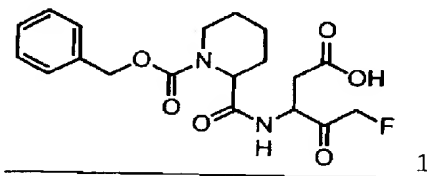
3. (currently amended) The compound of claim 2 having the following features: (a) R<sup>1</sup> is CH<sub>2</sub>F; (b) R<sup>2</sup> is CO<sub>2</sub>H or esters, amides or isosteres thereof; and (c) R<sup>3</sup> is hydrogen or an optionally substituted C<sub>1-6</sub> alkyl; ~~and (d) Ar is an optionally substituted aryl.~~

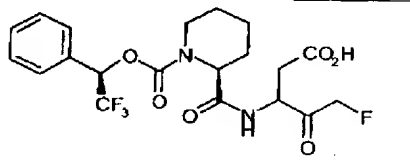
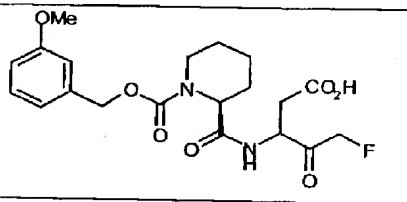
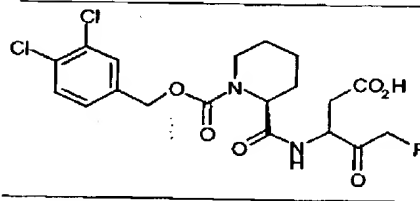
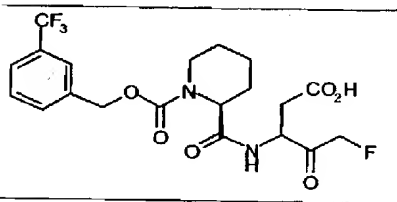
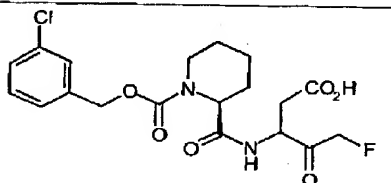
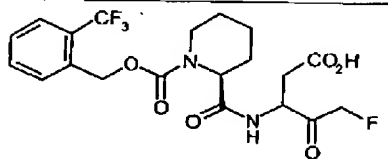
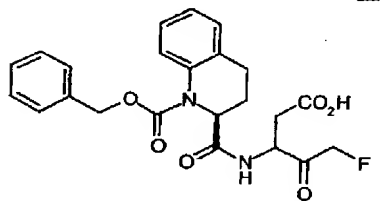
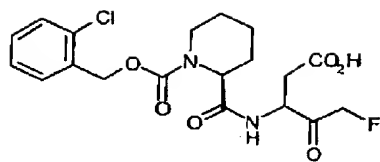
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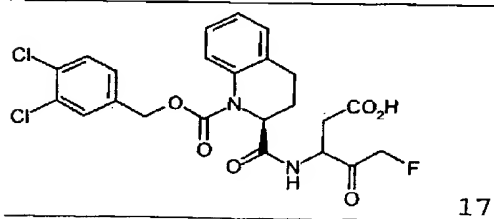
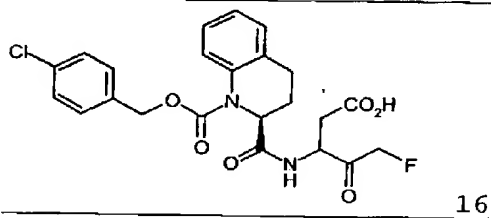
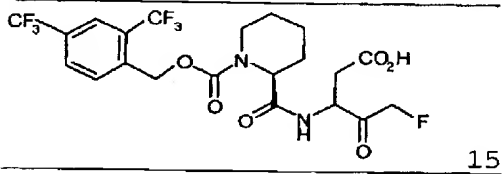
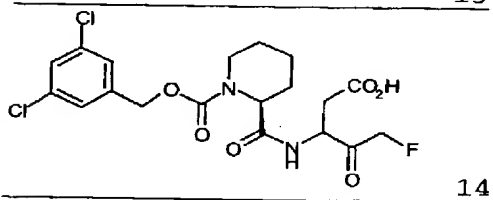
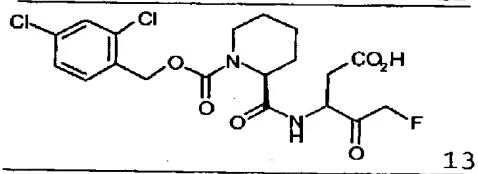
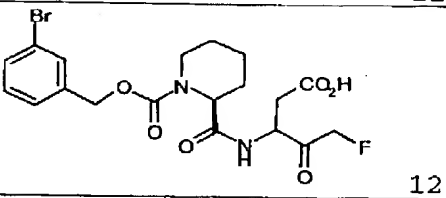
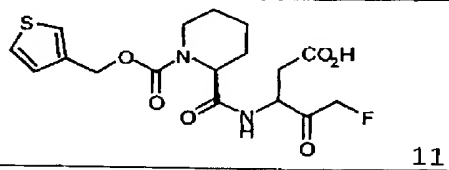
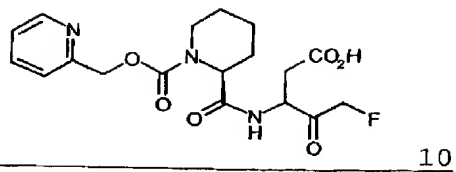
5. **(original)** The compound of claim 3 where Ring A is a tetrahydroquinoline ring.

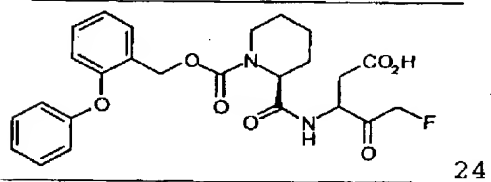
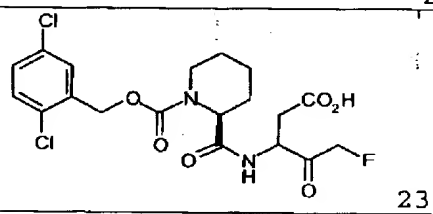
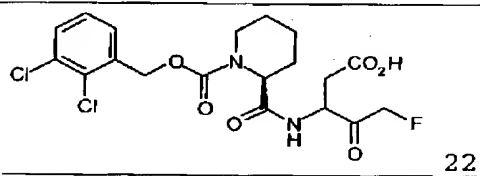
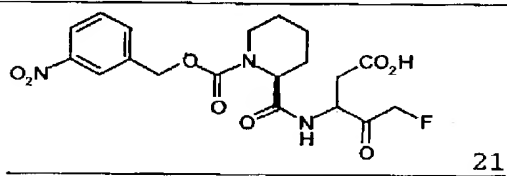
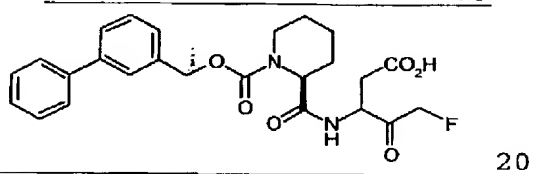
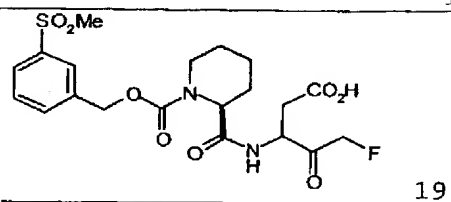
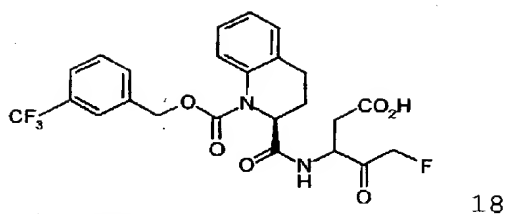
6. **(original)** The compound of claim 3 where Ring A is a tetrahydroisoquinoline ring.

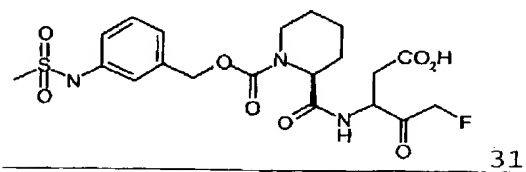
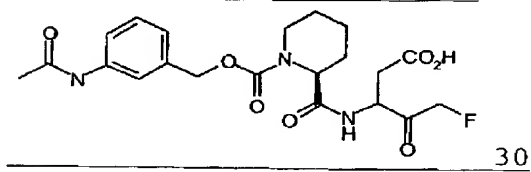
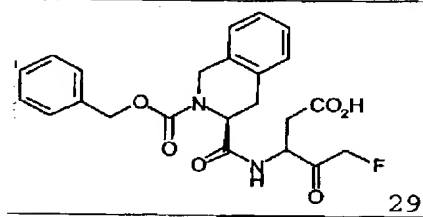
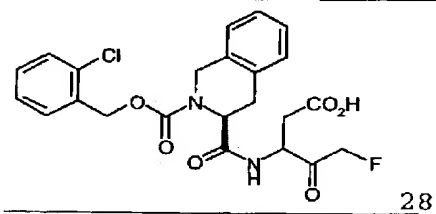
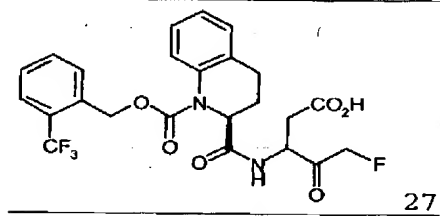
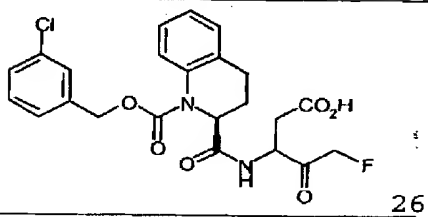
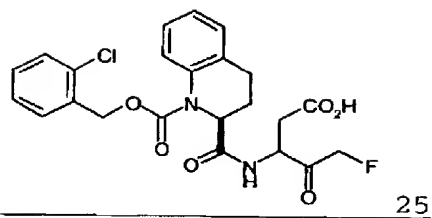
7. (currently amended) ~~The A compound of claim 1, wherein the compound is selected from the compounds listed in Table 1~~

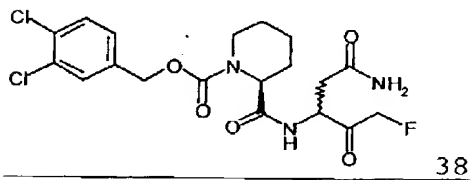
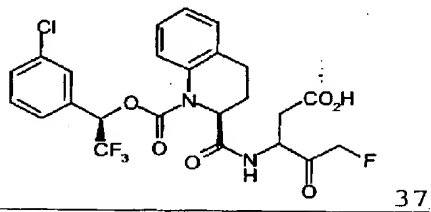
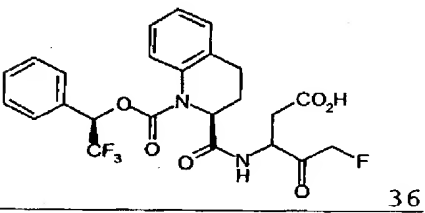
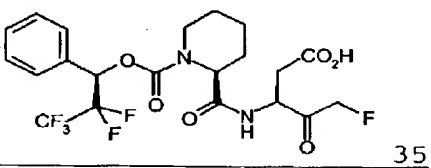
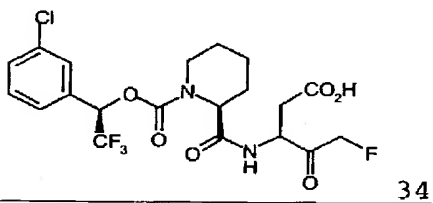
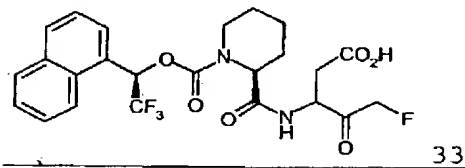
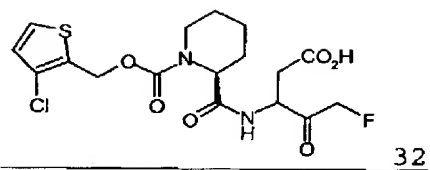


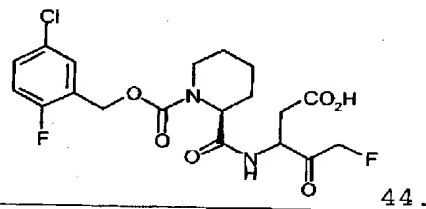
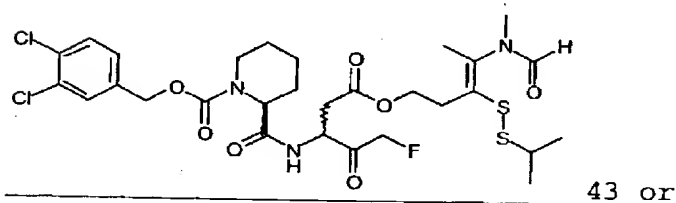
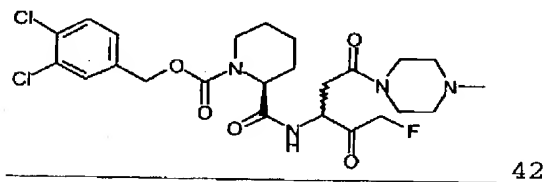
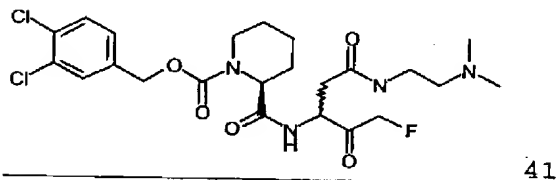
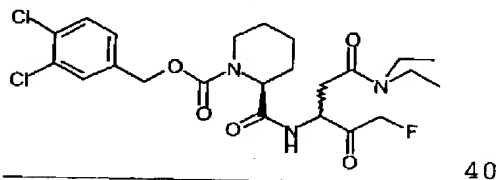
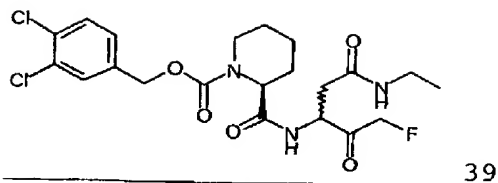






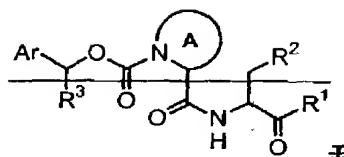






8. **(currently amended)** A method for treating a condition or disease state in mammals that is alleviated by treatment with a caspase inhibitor, comprising administering to a mammal in need of such a treatment a therapeutically effective amount of a compound according to any one of claims 1-3, 5-7 or 18-42 of formula I:-





wherein:

~~Ring A is an optionally substituted piperidine,~~

~~tetrahydroquinoline or tetrahydroisoquinoline ring,~~

~~R<sup>1</sup> is hydrogen, CHN<sub>3</sub>, R, or CH<sub>2</sub>Y,~~

~~R is an optionally substituted group selected from an aliphatic group, an aryl group, an aralkyl group, a heterocyclic group, or an heterocyclylalkyl group,~~

~~Y is an electronegative leaving group,~~

~~R<sup>2</sup> is CO<sub>2</sub>H, CH<sub>2</sub>CO<sub>2</sub>H, or esters, amides or isosteres thereof,~~

~~Ar is an optionally substituted aryl group, and~~

~~R<sup>3</sup> is hydrogen, an optionally substituted C<sub>1-6</sub> alkyl, F<sub>2</sub>, CN, aryl, or R<sup>3</sup> is attached to Ar to form an unsaturated or partially saturated five or six membered fused ring having 0-2 heteroatoms.~~

9-11. (cancelled).

12. **(currently amended)** The method of claim 8 wherein the disease is selected from an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a disease associated with cell death, an excess dietary alcohol intake disease, a viral mediated disease, uveitis, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active

hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, atopic dermatitis, scarring, graft vs host disease, organ transplant rejection, osteoporosis, leukemias and related disorders, myelodysplastic syndrome, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, haemorrhagic shock, sepsis, septic shock, burns, Shigellosis, Alzheimer's disease, Parkinson's disease, Huntington's disease, Kennedy's disease, prion disease, cerebral ischemia, epilepsy, myocardial ischemia, acute and chronic heart disease, myocardial infarction, congestive heart failure, atherosclerosis, coronary artery bypass graft, spinal muscular atrophy, amyotrophic lateral sclerosis, multiple sclerosis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, spinal cord injury, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, ~~or~~-Japanese encephalitis, ~~various forms of~~ liver disease, ~~including~~ alcoholic hepatitis, renal disease, polyaptic kidney disease, H. pylori-associated gastric and duodenal ulcer disease, HIV infection, tuberculosis, and meningitis.

13. (original) The method of claim 8 wherein the compound is used to treat complications associated with coronary artery bypass grafts.

14. **(currently amended)** ~~The A method of claim 8 wherein the compound is used for the preservation of cells, said method comprising the step of bathing the cells in a solution of the a compound or a pharmaceutically acceptable derivative thereof according to any one of claims 1-3, 5-7, or 18-42.~~

15. **(currently amended)** The method of claim 8-14, wherein ~~the compound or a pharmaceutically acceptable derivative thereof is used~~ the cells are in an organ for use in an organ transplant or for preserving in a blood products.

16. **(original)** The method of claim 8 wherein the compound is used as a component of immunotherapy for the treatment of cancer.

17. **(currently amended)** A pharmaceutical composition comprising a compound according to any of claims ~~1-7~~ 1-3, 5-7, or 18-42 and a pharmaceutically acceptable carrier.

18. (new) The compound of claim 1 where Ring A is a tetrahydroquinoline ring.

19. (new) The compound of claim 1 where Ring A is a tetrahydroisoquinoline ring.

20. (new) The compound of claim 1, wherein  $R^2$  is  $CO_2H$  or esters, amides or isosteres thereof.

21. (new) The compound of claim 20, wherein  $R^1$  is  $CH_2F$ .

22. (new) The compound of claim 1, wherein  $R^3$  is hydrogen or an optionally substituted  $C_{1-6}$  alkyl.

23. (new) The compound according to claim 1, wherein  $R^3$  is  $C_{1-6}$  haloalkyl.

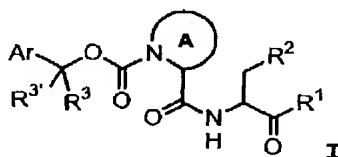
24. (new) The compound according to claim 23, wherein  $R^3$  is  $CF_3$ .

25. (new) The compound according to claim 23, wherein  $R^3$  is  $C_2F_5$ .

26. (new) The compound of claim 22, wherein  $R^1$  is  $CH_2F$ .

27. (new) The compound of claim 22, wherein  $R^2$  is  $CO_2H$  or esters, amides or isosteres thereof.

28. (new) A compound of formula I:



wherein:

Ring A is an optionally substituted piperidine ring;

$R^1$  is  $-H$ ,  $-CHN_2$ ,  $-R$ , or  $-CH_2Y$ ;

$R$  is an optionally substituted group selected from an aliphatic group, an aryl group, an aralkyl group, a heterocyclic group, or an heterocyclalkyl group;

$Y$  is an electronegative leaving group;

$R^2$  is  $CO_2H$ ,  $CH_2CO_2H$ , or esters, amides or isosteres thereof;

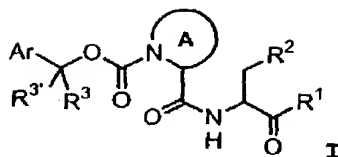
$Ar$  is an optionally substituted aryl group; and

$R^{3'}$  is  $-H$ , and  $R^3$  is  $-H$ , an optionally substituted  $C_{1-6}$  alkyl,  $CN$ , or aryl;

or  $R^3$  is attached to  $Ar$  to form an unsaturated or partially saturated five or six membered fused ring having 0-2 heteroatoms;

or  $R^3$  and  $R^{3'}$  are each  $-F$ ; provided that  $R^1$  is not  $-CH_2$ -tetazolyl.

29. (new) A compound of formula I:



wherein:

Ring A is an optionally substituted piperidine ring;

R<sup>1</sup> is hydrogen, CHN<sub>2</sub>, or -CH<sub>2</sub>Y;

Y is F, Cl, Br, I, -OSO<sub>2</sub>aryl, -OSO<sub>2</sub>C<sub>1-6</sub> alkyl, -OSO<sub>2</sub>CF<sub>3</sub>, -OR',  
-SR', -OC=O(R'), or -OPO(R<sup>4</sup>)(R<sup>5</sup>);

R<sup>2</sup> is CO<sub>2</sub>H, CH<sub>2</sub>CO<sub>2</sub>H, or esters, amides or isosteres thereof;

Ar is an optionally substituted aryl group;

R<sup>3</sup> is -H, and R<sup>3</sup> is -H, an optionally substituted C<sub>1-6</sub> alkyl, CN,  
or aryl;

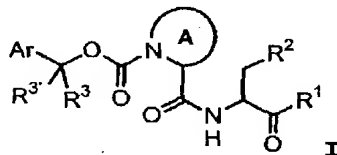
or R<sup>3</sup> is attached to Ar to form an unsaturated or partially  
saturated five or six membered fused ring having 0-2  
heteroatoms;

or R<sup>3</sup> and R<sup>3</sup> are each -F;

R<sup>4</sup> and R<sup>5</sup> are independently -R' or -OR'; and

R' is an aliphatic group, an aryl group, an aralkyl group, a  
carbocyclic group, an alkyl carbocyclic group, a heterocyclic  
group, or an alkyl heterocyclic group, wherein each group is  
optionally substituted.

30. (new) A compound of formula I:



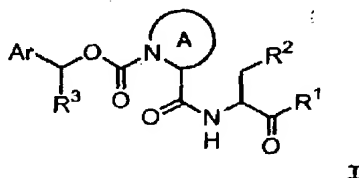
wherein:

Ring A is an optionally substituted piperidine ring;

R<sup>1</sup> is hydrogen, CHN<sub>2</sub>, R, or -CH<sub>2</sub>Y;

R is an unsubstituted aliphatic group, an optionally substituted aryl group, an optionally substituted heterocyclic group, or an optionally substituted heterocyclalkyl group;  
 Y is F, Cl, Br, I,  $-\text{OSO}_2\text{aryl}$ ,  $-\text{OSO}_2\text{C}_{1-6}\text{ alkyl}$ ,  $-\text{OSO}_2\text{CF}_3$ ,  $-\text{OR}'$ ,  $-\text{SR}'$ ,  $-\text{OC}=\text{O}(\text{R}')$ , or  $-\text{OPO}(\text{R}^4)(\text{R}^5)$ ;  
 $\text{R}^2$  is  $\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ , or esters, amides or isosteres thereof;  
 Ar is an optionally substituted aryl group;  
 $\text{R}^{3'}$  is  $-\text{H}$ , and  $\text{R}^3$  is  $-\text{H}$ , an optionally substituted  $\text{C}_{1-6}$  alkyl, CN, or aryl;  
 or  $\text{R}^3$  is attached to Ar to form an unsaturated or partially saturated five or six membered fused ring having 0-2 heteroatoms;  
 or  $\text{R}^3$  and  $\text{R}^{3'}$  are each  $-\text{F}$ ;  
 $\text{R}'$  is an aliphatic group, an aryl group, an aralkyl group, a carbocyclic group, a carbocyclalkyl group, a heterocyclic group, or an heterocyclalkyl, wherein each group is optionally substituted; and  
 $\text{R}^4$  and  $\text{R}^5$  are independently  $-\text{R}'$  or  $-\text{OR}'$ .

31. (new) A compound of formula I:



wherein:

Ring A is an optionally substituted piperidine ring;  
 $\text{R}^1$  is  $-\text{H}$ ,  $-\text{CHN}_2$ ,  $-\text{R}$ , or  $-\text{CH}_2\text{Y}$ ;  
 R is an optionally substituted group selected from an aliphatic group, an aryl group, an aralkyl group, a heterocyclic group, or an heterocyclalkyl group;  
 Y is an electronegative leaving group;  
 $\text{R}^2$  is  $\text{CO}_2\text{H}$ ,  $\text{CH}_2\text{CO}_2\text{H}$ , or esters, amides or isosteres thereof;

Ar is an optionally substituted aryl group; and  
R<sup>3</sup> is a C<sub>1-6</sub> haloalkyl.

32. (new) The compound according to claim 31, wherein R<sup>3</sup> is CF<sub>3</sub>.

33. (new) The compound according to claim 31, wherein R<sup>3</sup> is C<sub>2</sub>F<sub>5</sub>.

34. (new) The compound according to claim 29, wherein R<sup>1</sup> is -H.

35. (new) The compound according to claim 29, wherein R<sup>1</sup> is -CH<sub>2</sub>F.

36. (new) The compound of claim 29, wherein R<sup>1</sup> is -CH<sub>2</sub>OR<sup>1</sup>.

37. (new) The compound of claim 29, wherein R<sup>2</sup> is CO<sub>2</sub>H or esters, amides or isosteres thereof.

38. (new) The compound of claim 37, wherein R<sup>1</sup> is CH<sub>2</sub>F.

39. (new) The compound of claim 29, wherein R<sup>3</sup> is hydrogen or an optionally substituted C<sub>1-6</sub> alkyl.

40. (new) The compound of claim 39, wherein R<sup>1</sup> is CH<sub>2</sub>F.

41. (new) The compound of claim 39, wherein R<sup>2</sup> is CO<sub>2</sub>H or esters, amides or isosteres thereof.

42. (new) The compound of claim 41, wherein R<sup>1</sup> is CH<sub>2</sub>F.